EDITORIAL REVIEW

Glucose homoeostasis in chronic liver disease

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Introduction
The association between liver disease and abnormalities of carbohydrate metabolism has long been recognized. Although other defects exist, disturbance of blood glucose homoeostasis is most commonly noted. Hypoglycaemia is a practical problem only in acute hepatitis and fulminant hepatic failure, when it is a direct manifestation of massive acute loss of normal hepatocellular function. Fasting hyperglycaemia and impaired glucose tolerance occur in at least 50% of patients with established hepatic cirrhosis [1-3]. Naunyn [4] hypothesized that pancreatic insulin secretion was adequate but that some effect of the liver damage itself was responsible for the impairment of carbohydrate metabolism, leading to the name 'hepatogenous' diabetes. This hypothesis was supported by observation of elevated serum levels of immuno-reactive insulin in chronic liver disease of any aetiology [1, 2, 5, 6]. Doubts about the biological activity of immuno-reactive insulin in cirrhotic patients have recently been raised [7] and a reappraisal of current evidence is required.

Metabolic abnormalities
Most studies of patients with liver disease have concentrated on the fasted state or on the consequences of oral glucose administration. The effect of various degrees of alcoholic liver disease upon circulating hormones and metabolites over a 12 h period have been assessed [8]. A reasonable nutritional state was ensured before testing. In normal subjects the blood glucose concentration varied little through the 12 h, increments of 1-2 mmol/l occurring after meals. These mealtime responses were exaggerated (rises of 4-5 mmol/l) in patients with mild alcoholic liver disease, and in subjects with severe cirrhosis glucose values rose to around 11 mmol/l after breakfast and remained there throughout the day. Diurnal patterns of gluconeogenic precursors were also distorted. Blood lactate concentrations showed exaggerated post-prandial rises in mildly affected subjects. In patients with the most severe cirrhosis, fasting levels were raised and after breakfast were more than 2 mmol/l, remaining elevated for the rest of the day. The extent of hyperlactataemia in these cirrhotic patients showed a close correlation with two unrelated aspects of liver function, the elevation of serum bilirubin and the depression of serum albumin. Hyperlactataemia after a glucose load has been shown to correlate with the insulin response in chronic active hepatitis and cirrhosis [9]. It does not result from increased peripheral glycolysis, at least as assessed from the forearm model in cirrhotic man [10], but hepatic lactate clearance is impaired [9]. This point is of practical clinical importance in that lactic acidosis can be provoked relatively easily in patients with severe liver disease. In contrast, diurnal levels of another major gluconeogenic precursor, alanine, were lowered in both mild and severe cirrhotic groups. This could possibly be related both to the peripheral hyperinsulinism causing increased extrahepatic uptake and perhaps to a selective increase in hepatic extraction secondary to hyperglucagonaemia. The latter is less likely, especially in view of the demonstration of impaired hepatic clearance of glycerol in stable cirrhotic patients [11].

Hepatic glucose production
Estimates of basal glucose turnover rates in cirrhosis have varied. Perez et al. [12] and Cavallo-Perin et al. [13] were unable to demonstrate any abnormality. Decreased basal rates of glucose turnover have been observed in several studies ([14, 15]; D. M. Piniewska, A. J. McCulloch, M. G. Bramble, C. O. Record & K. G. M. M. Alberti, unpublished work). Any decreased hepatic glucose production in cirrhosis could relate to decreased rates of glyco-
Aetiology of the hyperinsulinaemia and insulin levels. C-peptide and insulin function is normal, C-peptide estimations should be an effect of insulin hypersecretion, impairment of insulin clearance or immuno-assay artifacts. Raised serum immunoreactive insulin levels could provide a more direct measure of insulin secretion, perhaps in response to the consequence of more severe hepatic disease, or merely represented wide confidence limits in the method of assessment. Further work using the same techniques upon a larger group of patients would be of great interest.

Measurement of serum insulin in cirrhotic subjects is complicated by the presence of a twofold elevation of serum proinsulin levels ([7]; R. Taylor, P. Gray, I. Hanning, L. Ashworth & K. G. M. M. Alberti, unpublished work). Proinsulin demonstrates approximately 50% cross-reactivity with insulin in the insulin radio-immunoassay and hence the serum insulin levels in cirrhotic subjects tend to be overestimated. However, because absolute proinsulin levels are low in comparison with absolute insulin levels, correction of measured immunoreactive insulin for the presence of proinsulin does not result in normalization of serum insulin levels [7]. Thus the hyperinsulinaemia is certainly a genuine phenomenon, even if overestimated.

Resistance to insulin action

A combination of raised serum true insulin and raised blood glucose both fasting and post-prandially, suggests that insulin action is impaired. This suggestion has been directly confirmed in cirrhotic subjects at least for peripheral tissues by using the hyperinsulinaemic, euglycaemic clamp technique [3, 13, 28]. The mechanism of tissue insensitivity to insulin action has been examined in adipocytes isolated from cirrhotic subjects. An important effect of aetiology of cirrhosis was observed. Adipocytes from alcoholic subjects have decreased insulin receptor number, insulin sensitivity and maximally stimulated rates of lipogenesis, whereas adipocytes from subjects with cryptogenic and primary biliary cirrhosis have normal insulin receptor number, decreased insulin sensitivity but supranormal maximally stimulated rates of lipogenesis [3]. A previous study of subjects with cirrhosis of unstated aetiology gave results similar to those of cryptogenic group [29]. Despite differences in adipocyte insulin receptor binding and insulin responsiveness, subjects with cirrhosis of any aetiology displayed marked insulin insensitivity in vivo [3]. Muscle tissue accounts for the larger part of insulin-medi-
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but that there is indeed some insulin insensitivity. Forearm studies suggest that there is indeed some insulin insensitivity. If it can be assumed that the regulation of carbohydrate metabolism in muscle and adipose tissue is similar, then it would appear that cell surface insulin receptor changes are regulated separately from the intracellular pathways of insulin action, and the latter are uniformly disturbed in hepatic cirrhosis.

The insulin counter-regulatory hormones could contribute to glucose intolerance by driving gluconeogenesis and/or glycogenolysis. Elevated immunoreactive glucagon levels have been reported in cirrhosis, and increased plasma cyclic AMP responses to glucagon infusion have been observed. However, diminished glucose responses to glucagon infusion of some insulin secretion rates are elevated, insulin clearance by the liver is impaired and insulin action at least upon peripheral tissues is impaired in subjects with hepatic cirrhosis. However, the main site of the insulin resistance is almost certainly the liver. The aetiology of the liver damage must also be considered when recruiting subjects for metabolic studies. It may be expected that future insights into the disturbances in carbohydrate metabolism in liver disease may be gained by examining concentrations of intermediary substrates and activity of rate-limiting enzymes in biopsy samples of both liver and muscle.

References

activities and peripheral insulin resistance in alcoholics with cirrhosis. *Journal of Hepatology, 1*, 277–290.


